Non-vitamin K oral anticoagulants for coronary or peripheral artery disease: a systematic review and meta-analysis of mortality and major bleeding

Nagy, Ádám ; Kim, Jun H ; Jeong, Myeong E ; Heo, Min H ; Putzu, Alessandro ; Belletti, Alessandro ; Biondi-Zoccai, Giuseppe ; Landoni, Giovanni

Abstract: INTRODUCTION Several high quality randomized controlled studies were recently published on non-vitamin K oral anticoagulants (NOACs) in patients with or at risk for coronary artery (CAD) or peripheral artery disease (PAD). While a reduction on cardiovascular event is known and an increase in moderate bleeding is expected, the effect of this strategy on survival is currently unknown. Accordingly, we performed a comprehensive systematic review and meta-analysis of randomized controlled trials to investigate the effect of NOAC on survival. EVIDENCE ACQUISITION We searched Pubmed, EMBASE, Cochrane Central Register, and Clinicaltrials.gov (last updated March 31st 2019). The primary endpoint was all-cause mortality at the longest reported follow-up. Coprimary endpoint was major bleeding according to the International Society on Thrombosis and Hemostasis (ISTH) criterion. EVIDENCE SYNTHESIS We included ten randomized controlled trials comparing NOACs versus control treatment (placebo, single platelet or dual antiplatelet therapy) enrolling 66665 patients with or at risk for CAD or PAD. NOACs were associated with a decreased risk of mortality (825/41655 [4.4%] versus 405/25010 [5.6%] RR 0.93 [95% CI: 0.87-1.00], P=0.04), and an increased risk for major bleeding (RR 1.62 [95% CI: 1.23-2.13], P=0.0005) when compared to control. Findings were robust to trial sequential, subgroup, and sensitivity analyses. Low doses NOACs were associated with a reduced mortality when compared to standard dose NOACs. CONCLUSIONS NOACs reduced all-cause mortality in patients with or at risk for CAD or PAD, even though they increased the risk of major bleeding. Future studies regarding the best doses of NOACs are warranted.

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REVIEW

Non-vitamin K oral anticoagulants for coronary or peripheral artery disease: a systematic review and meta-analysis of mortality and major bleeding

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ABSTRACT

INTRODUCTION: Several high quality randomized controlled studies were recently published on non-vitamin K oral anticoagulants (NOACs) in patients with or at risk for coronary artery (CAD) or peripheral artery disease (PAD). While a reduction on cardiovascular event is known and an increase in moderate bleeding is expected, the effect of this strategy on survival is currently unknown. Accordingly, we performed a comprehensive systematic review and meta-analysis of randomized controlled trials to investigate the effect of NOAC on survival.

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EVIDENCE SYNTHESIS: We included ten randomized controlled trials comparing NOACs *versus* control treatment (placebo, single platelet or dual antiplatelet therapy) enrolling 66665 patients with or at risk for CAD or PAD. NOACs were associated with a decreased risk of mortality (825/41655 [4.4%] *versus* 405/25010 [5.6%] RR 0.93 [95% CI: 0.87-1.00], P=0.04), and an increased risk for major bleeding (RR 1.62 [95% CI: 1.23-2.13], P=0.0005) when compared to control. Findings were robust to trial sequential, subgroup, and sensitivity analyses. Low doses NOACs were associated with a reduced mortality when compared to standard dose NOACs.

CONCLUSIONS: NOACs reduced all-cause mortality in patients with or at risk for CAD or PAD, even though they increased the risk of major bleeding. Future studies regarding the best doses of NOACs are warranted.

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KEY WORDS: Mortality; Coronary artery disease; Peripheral arterial disease.

Introduction

Cardiovascular diseases are one of the leading causes of morbidity and mortality worldwide with coronary artery (CAD) and peripheral artery diseases (PAD) representing the main burden for patients and national health systems.[1] Non-vitamin K antagonist oral anticoagulants (NOAC) were developed for being at least as effective as traditional anticoagu-

lants, with a more practical profile, such as oral administration with no need for routine monitoring or dose adjustment. NOACs are factor Xa or direct thrombin inhibitors. Ximelagatran was the first one, had limited success, but set the stage for the four widely approved and used NOACs: dabigatran, rivaroxaban, apixaban, and edoxaban. Guidelines are already including NOACs in the prevention of stroke in atrial fibrillation (except for the patients with mechanical prosthetic valves, or moderate to severe mitral stenosis),[2] in the prevention or treatment of venous thromboembolism (VTE) after elective total hip or knee replacement surgery or in case of recurrent VTE.[2, 3] Atherosclerosis is the common underlying pathophysiology in stable or unstable CAD or PAD.[1] An eroded or ruptured plaque can activate both platelet aggregation and the coagulation cascade, leading to a thrombus or embolism.[1] Unsurprisingly, atherosclerosis is associated with a high risk of cardiovascular adverse events and death. Aspirin inhibits platelet aggregation, reduces vascular events risk and mortality and is therefore widely used in primary and secondary cardiovascular prevention.[1, 4, 5] Additional P2Y12 inhibitor treatment offers a better survival in patients with recent acute myocardial infarction.[4] However, despite the single or dual antiplatelet therapy, the number of new or recurrent cardiovascular adverse events including death is considerably high.[6] Of note, there is no recommendation in guidelines (*e.g.* American Heart Association, European Society of Cardiology) against or towards the use of NOACs in this patient population. Published meta-analyses compared NOACs to vitamin K antagonist drugs in atrial fibrillation,[7-9] investigated NOACs in addition to single or dual antiplatelet therapy in acute coronary syndrome (ACS),[10] focused on patients with ischemic heart disease[11] and explored the role of Rivaroxaban in CAD.[12] Results are contradictory and there is lack of a comprehensive meta-analysis on this important field. The aim of our systematic review and meta-analysis is to evaluate the effect of NOACs *versus* placebo or single or dual antiplatelet therapy on survival and bleeding in patients with or at risk for CAD or PAD.

Evidence acquisition

We performed a systematic review and meta-analysis of randomized controlled trials (RCTs), according to the Cochrane methodology[13] and preferred reporting items for systematic reviews and meta-analyses PRISMA.[14]

Search strategy and selection criteria

Two trained investigators (AN, JHK) independently searched Pubmed, EMBASE, and the Cochrane Central Register of clinical trials together with Clinicaltrials.gov for recently completed but not published studies, dated up to March 31th, 2019. The search strategies for PubMed and EMBASE are available in the Supplementary Digital Material 1 (Supplementary Text File 1). The search strategies were designed to find any RCTs ever published with the utilization of NOACs in patients with or at risk for CAD or PAD. We checked the references of included studies to identify more eligible RCTs. No language restrictions were added. Articles were first screened as title and abstract and, if met the inclusion criteria, retrieved as a complete manuscript. Eligible studies had to meet the following PICOS criteria: Population: adult patients with the diagnosis or at high risk of CAD or PAD; Interventions: administration of NOACs and antiplatelet drugs or NOACs alone; Comparison intervention: placebo or single or dual antiplatelet therapy; Outcome: survival, or occurrence of clinically significant bleeding; Study design: randomized controlled trials. Disagreements between the two investigators about the eligibility of the article were solved by a third expert author.

Data analysis

Two trained authors (AN, JHK) separately gathered the baseline characteristics, outcome data, and additional relevant information from the selected studies. The primary endpoint was all cause of mortality at the longest reported follow-up. Coprimary endpoint was major bleeding according to the International Society on Thrombosis and Hemostasis (ISTH) criterion.[15] Secondary endpoints were the rate of cardiovascular death, acute myocardial infarction, hemorrhagic and non-hemorrhagic stroke, fatal bleeding, in-

tracranial bleeding, gastrointestinal bleeding, minor bleeding and need for hospital admission. In case of missing data of an outcome of interest, we contacted the corresponding authors. For the evaluation of the included trial risk of bias, we used the Cochrane methodology.[13] We assessed each study separately according to Cochrane's seven items as low, high or unclear risk of bias. We performed our analysis with RevMan 5.3. software (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata version 14.1 (StataCorp., College station, TX, USA). For dichotomous outcomes in primary and secondary endpoints, individual and pooled risk ratios were calculated via the Mantel-Haenszel method. We presented calculated risk ratio (RR) with 95% confidence intervals (CI). All reported P values are two-sided and the values equal or less than 0.05 were counted as significant. Heterogeneity among included studies was analyzed with Cochrane Q statistics and quantified with I^2. Fixed effect model was performed to create meta-analysis in the absence of significant heterogeneity, defined as P value >0.10 and I^2<40%.[13] We employed a random-effect model in case of significant heterogeneity. We performed a fixed-effects trial sequential analysis (TSA) with the intent of maintaining an overall 5% risk of type I error and a 20% risk of type II error, at a power of 80%. We assumed a relative risk reduction of 15% and derived the control event proportion from the dataset. The resulting required information size was further diversity (D^2)-adjusted. In the case of D^2=0, we performed a sensitivity analysis assuming a D^2=25%. The TSA Viewer software was used to perform TSA (TSA Viewer [Computer program], version 0.9.5.5 Beta, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, 2016).

Based on Cochrane methodology, we performed further subgroup analyses. In particular, we investigated the effect of low dose NOACs and standard dose NOACs. Subgroup differences were tested using χ^2 statistics. We considered the following mg/day dosages as low dose: rivaroxaban 5 mg/day; apixaban 5 mg/day; dabigatran 100-150 mg/day. The following were considered standard dose: rivaroxaban 10 mg/day; apixaban 10 mg/day; dabigatran 220 mg/day.[16, 17] These drugs are used in various clinical indications, therefore it was hard to create a threshold value between the two subgroups. We created these categories considering the dosages of the included studies and the international recommendations.

Our study was preregistered in PROSPERO (reg. No. 2019-CRD42019119717).

Evidence synthesis

Our search strategy identified 761 records (Figure 1). Major exclusion papers are presented in Supplementary Digital Material 2 (Supplementary Table I). Ten studies were eligible for inclusion into the final analyses (Table I).[4-6, 18-24]

In summary, the data of 66,665 (41,655 experimental and 25,010 control group) patients were included. The most commonly studied study drug was rivaroxaban (5 out of 10 studies[4, 6, 20, 21, 24]) followed by apixaban (3 studies[18, 19, 22]), and dabigatran (2 studies[5, 23]). The studied settings were recent ACS in 7 articles[4, 18-23] and were stable CAD or PAD,[6] myocardial injury after non-cardiac surgery (MINS),[5] and heart failure with CAD[24] in each other articles. Placebo was used as control treatment in 8 studies,[5, 18-24] the

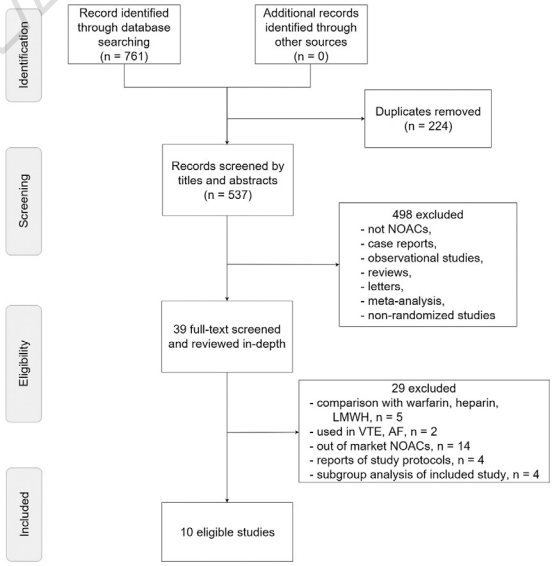

Figure 1.—Flow chart of study selection.
NOACs: non-vitamin K oral anticoagulants; LMWH: low molecular weight heparin; VTE: venous thromboembolism.

TABLE I.—*Characteristics of included studies.*

	Study abbreviation	Population	Study period	Patient etiology
Alexander *et al.* (2009)[18]	APPRAISE	1691	2006.05-2007.10	Recent ACS with high risk factors
Alexander *et al.* (2011)[19]	APPRAISE-2	7392	2009.03-2010.11	Recent ACS with high risk factors
Devereaux *et al.* (2018)[5]	MANAGE trial	1754	2013.01-2017.07	Myocardial injury after non-cardiac surgery
Eikelboom *et al.* (2017)[6]	COMPASS trial	27,395	2013.03-2016.05	Stable atherosclerotic vascular disease
Mega *et al.* (2009)[20]	ATLAS ACS-TIMI 46	3491	2006.11-2008.09	Recent ACS
Mega *et al.* (2012)[21]	ATLAS ACS-TIMI 51	15,526	2008.11-2011.09	Recent ACS
Ogawa *et al.* (2013)[22]	APPRAISE-Japan	149	2009.04-2010.11	Recent ACS with high risk factors
Ohman *et al.* (2017)[4]	GEMINI-ACS-1	3037	2015.04-2016.10	After ACS
Oldgren *et al.* (2011)[23]	RE-DEEM	1861	2008.03-2009.10	Recent MI, and at high risk of new ischemia
Zannad *et al.* (2018)[24]	COMMANDER HF	5022	2013.09-2017.10	Recent worsening heart failure, reduced EF, CAD, and no AF

NOAC: non-vitamin K oral anticoagulant; ACS: acute coronary syndrome; EF: ejection fraction; CAD: coronary artery disease; AF: atrial fibrillation; APX: apixaban; RIV: rivaroxaban; ASA: acetyl salicylic acid; DABI: dabigatran.

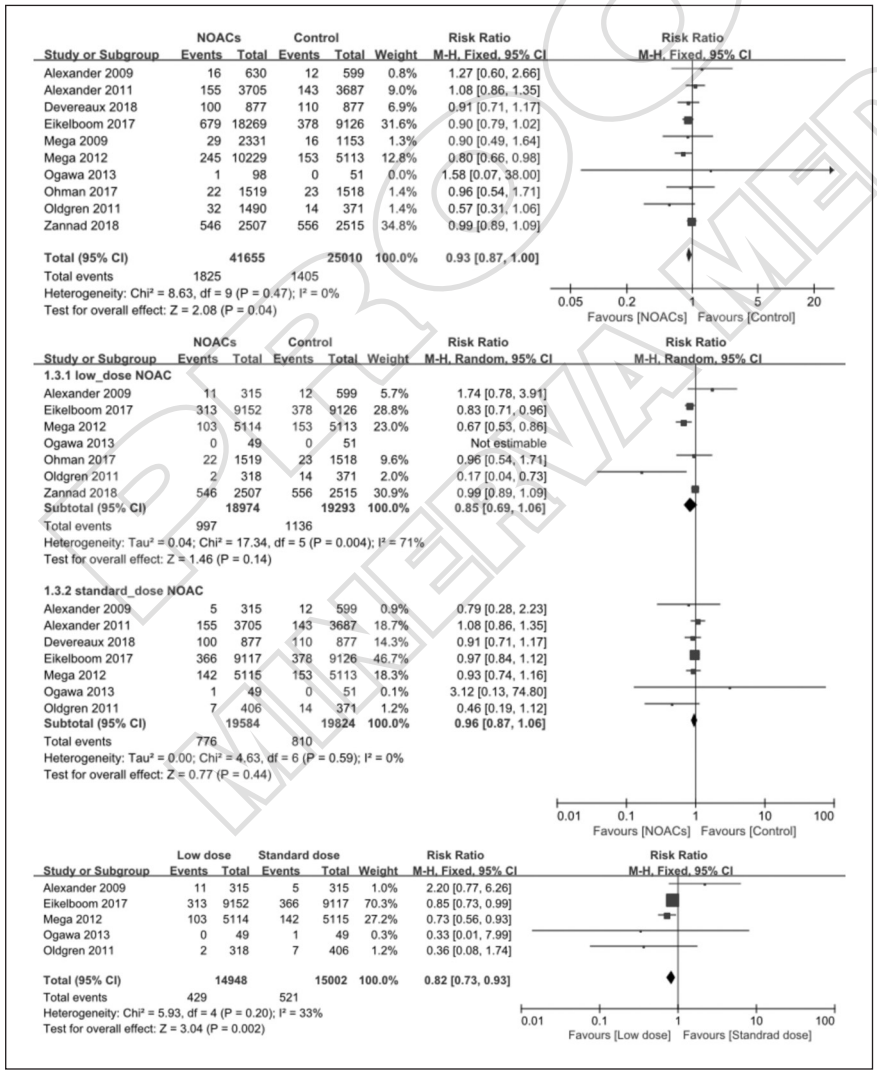

Figure 2.—Forest plots of all-cause mortality at the longest follow-up.[4-6, 18-24] NOACs: non-vitamin K oral anticoagulants.

Type of NOAC	Study groups	NOAC patients	Control atients
APX	5 mg APX /10 mg APX / 20 mg APX / Placebo	630	599
APX	10 mg (5 mg in decreased renal function) APX / Placebo	3705	3687
DABI	220 mg DABI / Placebo	877	877
RIV	5 mg RIV + ASA / 10 mg RIV / Placebo + ASA	18269	9126
RIV	5, 10, 20 mg RIV / 5, 10, 15, 20 mg RIV + thienopyridine / Placebo	2331	1153
RIV	5 mg RIV / 10 mg RIV / Placebo	10229	5113
APX	5 mg APX / 10 mg APX / Placebo	98	51
RIV	5 mg RIV + P2Y12inhibitor / ASA + P2Y12inhibitor	1519	1518
DABI	100 mg DABI / 150 mg DABI / 220 mg DABI / 300 mg DABI / Placebo	1490	371
RIV	5 mg RIV / Placebo	2507	2515

remaining two[4, 6] used aspirin. Standard medication of artery diseases was maintained during the study period, therefore none of the comparator groups were totally free of antiplatelet (Aspirin and/or P2Y12 antagonists) treatment. Only one study[6] had an experimental arm without administration of antiplatelet agents. Eight studies[4, 6, 18, 20-24] used a low dose and 8 studies[5, 6, 18-23] used a standard dose of NOAC. All studies had low risk of bias (Supplementary Digital Material 3: Supplementary Table II).

Mortality

Overall, administration of NOACs significantly decreased the risk of death compared to control treatment (10 RCT, 1825/41,655 [4.4%] NOAC, 1405/25,010 [5.6%] control, N.=66,665, RR 0.93 [95% CI: 0.87-1.00], P=0.04, I^2=0%) (Figure 2).[4-6, 18-24] Final analysis is conclusive according to TSA (Supplementary Digital Material 4: Supplementary Figure 1).

Overall, we found significant difference in the comparison of low dose *versus* standard dose of NOACs (5 RCT, 429/14,948 [2.9%] low dose, 521/15002 [3.5%] standard dose, N.=29,950, RR 0.82 [0.73-0.93], P=0.002, I^2=33%). Sequential removing each trial did not change magnitude and direction of treatment effect (lowest RR 0.81 [95% CI: 0.71-0.92], P=0.001, I^2=0%) with the removal of Alexander *et al.* and (highest RR 0.86 [95% CI: 0.74-0.99], P=0.04, I^2=35%) with the removal of Mega *et al.* Subgroup analysis by low dose and standard dose of NOACs found no difference between treatment and control in case of low doses (7 RCT, 997/18974 [5.3%] NOAC, 1136/19293 [5.9%] control, N.=38267, RR 0.85 [95% CI: 0.69-1.06], P=0.14, I^2=71%) and also in case of standard doses (7 RCT, 776/19,584 [4.0%] NOAC, 810/19,824 [4.1%] control, N.=39,408, RR 0.96 [95% CI: 0.87-1.06], P=0.44, I^2=0%) (Figure 2).

Major bleeding

Patients treated with NOACs had an increased risk of major bleeding according to ISTH when compared to control group (8 RCT, 681/29,095 [2.3%] NOAC, 327/18,744 [1.7%] control, N.=47,839, RR 1.62 [95% CI: 1.23-2.13], P=0.0005, I^2=60%) (Figure 3).[4-6, 18-24] TSA analysis revealed this inconclusive (Supplementary Digital Material 5: Supplementary Figure 2).

Comparison of different doses of NOAC revealed, that standard dose significantly increased the risk of major bleeding (4 RCT, 216/10,253 [2.1%] low dose, 271/9887 [2.7%] standard dose, N.=20,140, RR 0.78 [95% CI: 0.66-0.93], P=0.007, I^2=6%) (Supplementary Digital Material 6: Supplementary Table III). Subgroup analysis found that, both low dose (6 RCT, 329/14279 [2.3%] NOAC, 244/14180 [1.7%] control, N.=28,459, RR 1.35 [95% CI: 1.15-1.59], P=0.0003, I^2=0%) and standard dose (6 RCT, 428/14,469 [3.0%] NOAC, 260/14711 [1.8%] control, N.=29180, RR 1.66 [95% CI: 1.43-1.93], P<0.0001, I^2=38%) increased the risk of major bleeding compare to control treatment (Table II).

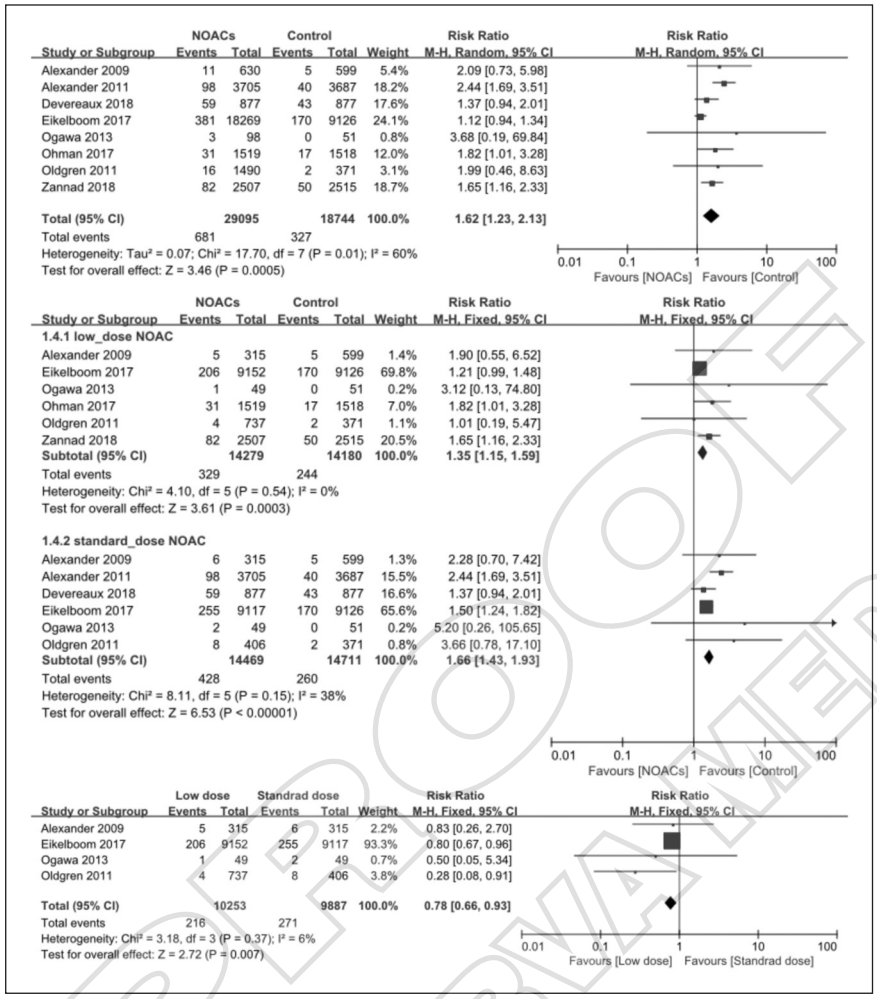

Figure 3.—Forest plots of major bleeding according to International Society on Thrombosis and Hemostasis (ISTH).[4-6, 18-24]
NOACs: non-vitamin K oral anticoagulants.

Secondary outcomes

Meta-analyses of secondary outcomes revealed the following results. The risk rate of cardiovascular death, acute myocardial infarction, and stroke (hemorrhagic and non-hemorrhagic) was significantly higher in the control group compared to NOAC treatment group. The risk of intracranial bleeding, gastrointestinal bleeding, and minor bleeding was increased among patients treated with NOACs compare to control (Table II, Supplementary Digital Material 7: Supplementary Figure 3).

Sensitivity analysis performed by sequential removal of each included study did not change the magnitude and direction of the overall results and are reported in Supplementary Digital Material 8 (Supplementary Table IV). Egger's test revealed publication bias in the minor bleeding analysis (P=0.035) (Table II, Supplementary Digital Material 9: Supplementary Figure 4), the remaining analyses are free of publication bias (Table II, Supplementary Digital Material 9).

Limitations of the study

One limitation of our study is that we included studies which used a different definition of major bleeding. The majority of studies used ISTH definition of major bleeding, but some of the studies used TIMI definition[20, 21] and after unsuccessful attempts to contact the authors we excluded those studies from this outcome anal-

TABLE II.—*Summary of findings (overall and subgroup) and Egger's Test.*

Outcome of interest	Number of included trials	Participants, N.	NOAC group		Control group		Risk ratio (95% CI)	P for significance	I^2 (%)	Egger's test P value
			Events	Total	Events	Total				
All-cause mortality at longest follow-up	10	66,665	1825	41,655	1405	25,010	0.93 (0.87-1.00)	0.04	0	0.919
Low dose	7	38,267	997	18,974	1136	19,293	0.85 (0.69-1.06)	0.14	71	
Standard dose	7	39,408	776	19,584	810	19,824	0.96 (0.87-1.06)	0.44	0	
Major bleeding (ISTH)	8	47,839	681	29,095	327	18,744	1.62 (1.23-2.13)	0.001	60	0.113
Low dose	6	28,459	329	14,279	244	14,180	1.35 (1.15-1.59)	<0.001	0	
Standard dose	6	29,180	428	14,469	260	14711	1.66 (1.43-1.93)	<0.001	38	
Cardiovascular death	9	63,181	1251	39,324	1032	23,857	0.90 (0.84-0.99)	0.01	0	0.668
Low dose	7	38,686	754	19,393	859	19,293	0.87 (0.71-1.06)	0.18	58	
Standard dose	7	39,408	494	19,584	539	19,824	0.92 (0.82-1.04)	0.19	0	
Acute myocardial infarction	10	66,665	1227	41,655	905	25,010	0.88 (0.80-0.96)	0.003	0	0.559
Low dose	7	38,686	561	19,393	624	19,293	0.90 (0.80-1.01)	0.07	0	
Standard dose	7	39,408	591	19,584	694	19,824	0.86 (0.77-0.96)	0.006	0	
Stroke	10	66,665	391	41,655	327	25,010	0.69 (0.53-0.91)	0.008	44	0.146
Low dose	3	19,486	84	9938	146	9548	0.57 (0.44-0.74)	<0.001	0	
Standard dose	5	31,102	155	15,564	197	15,538	0.79 (0.64-0.97)	0.02	22	
Fatal bleeding	7	60,198	67	37,817	29	22,381	1.37 (0.89-2.11)	0.15	0	0.529
Low dose	6	37,772	32	19,078	29	18,694	1.07 (0.64-1.77)	0.80	0	
Standard dose	6	39,961	44	19,269	35	20,692	1.63 (0.68-3.91)	0.28	60	
Intracranial bleeding	7	58,010	120	36,719	35	21,291	1.91 (1.31-2.77)	0.001	0	0.327
Low dose	5	33,564	43	16,837	29	16,727	1.47 (0.92-2.35)	0.10	18	
Standard dose	6	40,455	77	19,535	35	20,920	2.20 (1.48-3.28)	<0.001	0	
Gastrointestinal bleeding	5	32,388	326	21,364	83	11,024	2.00 (1.57-2.54)	<0.001	0	0.507
Low dose	4	20,400	179	10,253	77	10,147	2.53 (1.31-4.91)	0.006	54	
Standard dose	5	21,788	136	10,764	83	11,024	1.97 (1.25-3.09)	0.003	31	
Minor bleeding	8	60,414	2080	38,518	663	21,896	1.63 (1.49-1.77)	<0.001	21	0.035
Low dose	5	32,750	984	16,571	566	16,179	1.66 (1.50-1.83)	<0.001	0	
Standard dose	6	38,494	1037	19,269	657	19,225	1.77 (1.43-2.19)	<0.001	56	

NOAC: non-vitamin K oral anticoagulant; ISTH: International Society on Thrombosis and Hemostasis.

ysis. Patients were at different risk profiles in the included trials, since we chose to involve a wide spectrum of diseases (although they shared same pathogenesis) in our population. The comprehensive range of disease could cause the significant heterogeneity among the results of the trials. Two further limitation can be the distinction of different NOAC doses with creating low and standard dose and also the comparability of different type of NOACs with low and standard doses. Different concomitant antiplatelet therapies were used in the included studies, therefore, our population is heterogenic in that aspect. The recruiting time of the first and last included study were more than 10 years apart, which could have caused changes in many aspects. Another possible limitation of all the studies included in this meta-analysis is that they were all supported by pharmaceutical companies. Furthermore, no study used competing risk models (CRM) for the main analysis, and we also extracted raw event estimates. Therefore, CRM was not applied to our analysis either. While heterogeneity was mild for main comparative analyses, it varied substantially depending on outcome or control group, with more severe heterogeneity when appraising endpoints with different definitions. Finally, no multivariate meta-analysis method was applied in our work.

Conclusions

Our results show that NOACs decrease all-cause mortality in CAD and PAD, but they also increase the risk of major bleeding by ISTH criteria. Results were confirmed in most sub-analyses and sensitivity analyses.

The only recent meta-analysis of NOACs

which included patients similar to those of our meta-analysis was limited to only one NOAC agent (four trials on rivaroxaban were included).[12] As far as we know, our study is the first which encompasses all the NOACs into the analysis. We included all the studies performed over more than ten years, gathered all the reports on all marketed NOACs, even including sensitivity analyses with those which are currently not on the market and had results showing similar magnitude and direction that the main analyses (Supplementary Digital Material 10: Supplementary Table V). Studies with out of market NOACs are indicated in the Supplementary Digital Material 2.

All the studies we included (66,665 patients overall) were high-quality RCTs, and at low risk of bias. Previous meta-analyses of NOACs usually included only patients with atrial fibrillation or venous thromboembolism (VTE), or belonging to a specific age population.[7, 25-27] Cohen *et al.* performed a systematic review and meta-analysis of NOACs in VTE, reporting that the risk of VTE or VTE-related death was lower in NOACs and warfarin INR 2.0-3.0 when compared with aspirin.[25] Hulle *et al.* also compared NOACs with VKAs in VTE and concluded that the efficacy of NOACs was comparable to VKA and that the risk of bleeding complication was reduced.[26] Zelniker *et al.* compared NOACs with warfarin in patients with atrial fibrillation, to find out if there was effect modification by CAD status.[7] The effect of NOACs was beneficial compared to warfarin and was not different by the presence or absence of the CAD. Sardar *et al.* compared NOACs with conventional treatment (Warfarin, aspirin, enoxaparin, VKA, or placebo) in patients aged 75 and older with various diseases, and reported that NOACs did not cause excessive bleeding and were associated with equal or greater efficacy than conventional treatment.[27]

These favourable results of NOACs might be caused by possible merits over other anticoagulants. First, NOACs target specific factors in the coagulation cascade (either factor Xa or thrombin), unlike warfarin and VKAs.[28] Second, NOACs do not completely inhibit the target protease. The inhibition of thrombin molecules increased proportionally as the concentration of NOACs increases. If more thrombin is generated, the level of free (active) thrombin will increase at any given concentration of NOACs. Thus, if there are sufficiently strong procoagulant stimulus, the inhibitory effect could be overcome.[28] This might be the reason why a lower incidence of intracranial bleeding was reported with some NOACs than VKAs in several studies.[29-31] However, the overall clinical effect of this property seems to be difficult to predict.[28]

In our analysis, NOACs decreased all-cause mortality even though they increased major bleeding. Similarly, the effects of NOACs on secondary endpoints showed both favourable and unfavourable results. Effects of NOAC on bleeding seems to be dose-dependent, according to the subgroup analysis of low dose *versus* standard dose in major bleeding and intracranial haemorrhage. When comparing low dose NOACs *versus* standard dose NOACs we found that low doses were associated with reduced mortality, reduced major bleeding, and stroke. Using a low dose of NOACs in these setting seems reasonable according to the finding of this study but considering that there is still debate about dosing in other settings,[32-34] we could not conclude which dosage is beneficial. Maybe there shall be a "Goldilocks" dose which won't increase the risk of bleeding, although still reduces mortality. Or there may be a need for different doses for a different population (*i.e.*, standard dose NOAC for AMI patients and low dose for other patients).

We did not want to include a comparison of warfarin with NOACs, because warfarin was used almost exclusively in atrial fibrillation which was not included in our current research. However, warfarin might have a role in CAD or PAD, like NOACs, and may have some advantages compared to NOACs. The beneficial effects of warfarin in cardiovascular disease were previously reported.[35-37] Also, it has cheap, easy to get, well-known antidotes (vitamin K, fresh frozen plasma and coagulation factors concentrates). In contrast, the antidotes for NOACs are not available, recently approved, or very expensive.[38-40] When bleeding occurs, the availability of an antidote may be important to the outcome.

In conclusion, NOACs reduced all-cause mor-

tality in patients with or at risk for CAD or PAD, even though it increased the risk of major bleeding. Future study regarding the best doses of NOACs is warranted.

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